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Review

Mast cells, mediators, and symptomatic activation

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Abstract: Mast cells (MC) are central effectors of allergic disease and distinct subsets with varying amounts of tryptase, chymase, and carboxypeptidase A3, and cathepsin G is distributed throughout the body. Their involvement in a diverse range of non-allergic illnesses mediated by a complex range of preformed and newly synthesized mediators is now increasingly recognized. The latter especially include conditions under the umbrella term of mast cell activation syndrome. In allergic disease, much has been written about the mechanisms by which the early and rapidly acting mediators produce both localized and systemic allergic symptoms. The role of chymase is presently underappreciated but there is increased awareness that MCs contain significant amounts of preformed TNF alpha and synthesize and releases a wide range of inflammatory cytokines such as interleukins (IL) 1β, IL6, IL31, and IL33. These can aggravate itching and perpetuate inflammation and likely contribute to the late constitutional symptoms seen in allergic reactions. Importantly, their involvement helps to clarify the role of MCs in stress and non-parasitic infections. Presently, unexplained is the increasing incidence of significant acute allergic reactions within a relatively short time frame. In this context, there is increasing interest in the environmental, menstrual, endocrine, circadian, and psychological factors that influence MC activation as well as the endocrine pathways involving the renin angiotensin system that oppose hypotension. In non-allergic diseases with normal numbers of MCs, reduced thresholds for activation may be produced by various combinations of life and dietary factors. Diagnosing these conditions is difficult but may be helped by urinary analysis of prostaglandin metabolites. The investigation and management of mastocytosis with and without mutations of c-kit is also relevant to allergic disease and the new medications used may also be helpful in idiopathic anaphylaxis. This knowledge may open a new chapter in human diseases and mast cell regulation.

Keywords: mast cells; anaphylaxis; renin & angiotensin system; genes of renin angiotensin system; endothelial nitric oxide; c-KIT; mast cell disorders; mastocytosis

Abbreviations: ACE: angiotensin converting enzyme; RAS: renin angiotensin system; AII: angiotensin-2; AI: angiotensin-1; PAF: platelet activating factor; eNO: endothelial nitric oxide; ATR-1: angiotensin-2 receptor; BK: bradykinin; BP: blood pressure; C5a: complement protein C5a; C3a: complement protein C3a; mRNA: messenger RNA; IgE: Immunoglobulin E

1. Introduction

Mast cells (MC) are widely distributed and have central roles in allergic disease as well as an increasing range of illnesses caused by either raised numbers of these cells and/or lower thresholds for activation and degranulation. They contain numerous mediators, some of which are preformed and some newly synthesized on activation. While many of the preformed mediators are critical for the acute cardiorespiratory, cutaneous, and gastrointestinal symptoms some of the cytokines also contribute to the late phase reaction and many of the constitutional symptoms. The role of some of the mediators such as chymase is also being redefined along with a range of cofactors that can facilitate MC activation.

Anaphylaxis can be defined as an acute systemic hypersensitivity reaction resulting from the release of mast cell histamine with other mediators that have widespread effects upon 2 or more organs (skin, lungs, and gastrointestinal and cardiovascular systems) [1]. While many cases of anaphylaxis are caused by re-exposure to allergen and cross linkage of adjacent specific IgE on the MC surface, some arise from specific IgG and others from direct activation of normal or raised numbers of MCs. Numerous factors are now considered to modulate the severity of an allergic reaction. These include genetic, endocrine and nutritional variables, enzymes and proteins involved blood pressure regulation and even stress and concomitant drug use.

In the U.K, 2% of the adult population carries adrenaline due to prior anaphylactic reactions [2]. Anaphylaxis is increasing on a global scale without explanation. Indeed a 9-year Australian study showing a 150% increase in anaphylaxis admissions and a 300% increase in fatalities, especially in children [3]. Demographically, there appears to be a very high incidence of anaphylaxis in young children < 5 years from food allergies and in pre-menopausal women. A 15-year study in the UK confirmed this trend, and showed a 7-fold increase in hospital admission especially for young children but without a clear explanation for the increase [4–7]. Regardless, subjects usually repeat their prior allergic reactions on further exposure unless the allergen dose is small [1,4,8].

2. The central role of Mast cells in allergy anaphylaxis, and mast cell disorders

2.1. Clinical and genetic aspects of allergic disease and anaphylaxis

MC activation can result in clinical symptoms ranging from mild cutaneous effects (Grade I) to worsening bronchospasm, angioedema and cardiac arrest from profound hypotension and circulatory collapse (Grade 4) as per Terr's original Classification 1985 [8]. Thankfully, severe anaphylaxis is a relatively rare but the manifestations can go unrecognized in some cases. Autopsy studies have shown 80% of deaths to have upper airway oedema with secondary pulmonary hyperinflation and circulatory collapse as their only features [9,10]. Unsurprisingly, prior cardio-respiratory disease and poorly controlled asthma increases the risk of death in adults. The presence of asthma in small children with allergic reactions is a significant risk factor for a severe outcome, as small children have a lower

lung capacity with histamine-induced bronchoconstriction producing greater respiratory difficulty than seen for adults [5,6,11].

Presently, there are few links between anaphylaxis and specific "allergy genes" [2]. Additionally, the host cofactors, which influence the severity of reactions that remain ill-defined [11–13]. Surprisingly, some subjects experiencing near-fatal anaphylaxis have low levels of circulating allergen-specific IgE, while others with higher levels have no symptoms upon exposure [14]. Unfortunately, many causes of anaphylaxis remain unidentified although foods are a leading cause in children, whereas venom or drugs account for the majority of adult cases [15,16]. In the hospital setting, the risk of cardiac arrest and death was greater in obese patients, those with coronary artery disease or in those taking beta-blockers or ACE-inhibitor drugs. The commonest triggers were antibiotics, neuromuscular blocking drugs, the anti-septic chlorhexidine, patent blue dye, blood products and gelatin [17]. Serum tryptase analysis can help in supporting a diagnosis of anaphylaxis but confirm only mast cell activation and the clinical history is critical. This is especially so in the case of patients manifesting the symptoms of allergic mediator release but without demonstrable specific IgE.

2.2. Mast cell subtypes and distribution

It is now abundantly clear that mast cells (MC) are distributed throughout the body including the myocardium and in the retina where they have been noted in the bursa premacularis and especially in certain ocular conditions [18]. Within the central nervous system, they are located in several areas and can influence stress mediated allergic type reactions [19] and are also involved in regulating sleep [20]. They are central players in the initiation and progression of an allergic immune response and critical in the majority of anaphylactic reactions [21]. They are also critically important in all types of mast cell activation syndrome [22–24] and especially in mastocytosis [22,24] where there is an increase in the numbers of irritable MCs. Developmentally, MC are derived from CD34+/CD117+/CD13+ multipotent, hematopoietic progenitors stimulated by the action of stem cell factor on the c-kit transmembrane tyrosine kinase [25,26]. They are broadly divided into mucosal and tissue MCs based on morphological differences and variations in tryptase, chymase, cathepsin G, and carboxypeptidase A3 [27,28]. As such connective tissue MCs are located predominantly in the skin and submucosa of the gastrointestinal tract mucosa and produce all four proteins while mucosal MCs are found in the alveoli and mucosa and produce only tryptase [26,29–31]. There are also differences in the precise amounts of allergic mediators and cytokines held and released by these subsets, which likely reflect subtle differences in their primary function [32].

2.3. Mast cell release of preformed mediators

It is now clear that complexes of IgE and FcεR remain on the surface of the MC for a long time and are the main mechanism of sensitization to the allergen. MCs are activated by allergen cross-linking of pre-existing allergen specific IgE bound to FcεRI, by non-IgE mediated mechanisms [33] and by IgG anti-IgE antibodies evident in some patients with atopic dermatitis [34]. These results in rapid release several preformed mediators held in numerous granules as part of the initial allergic response [35] (Table 1). Important amongst these are histamine, tryptase, chymase, heparin, tumor necrosis factor alpha (TNFα), platelet activating factor (PAF), and others detailed in Table 2. The action of histamine is well known and includes smooth muscle contraction leading to vasodilation and

bronchoconstriction and disruption of the micro-circulation leading to angioedema and hypotension and central nervous system symptoms [36–38]. Tryptase promotes inflammation and stimulates fibrin formation as well as the conversion of IL33 into a more active form [39]. Importantly, MCs are the only cells that hold preformed TNFα [40], which is rapidly secreted and can contribute to attraction and activation of several inflammatory cells [41], including T cells [42–44]. It is possible that TNFα contributes to the exhaustion, drowsiness and flu-like sensation that follows acute severe allergic reactions although histamine stimulation through the H3 receptor is likely also involved [45].

Table 1. Mast cell mediators.

Pre-stored Mediators and enzymes	**Actions**
Histamine	Vasodilation, hypotension, itch
5-Hydroxytryptamine	Vasoconstriction
Tryptase	Inflammation, tissue damage, pain
Chymase	Neutralises bradykinin, angiotensin II synthesis
Heparin	Angiogenesis, anticoagulant, stabilizes nerve growth factor
Kinogenases	Synthesis of vasodilatory kinins, pain
Carboypeptidase A	Peptide processing
Metalloproteinases	Tissue damage
Phospholipases	Arachidonic acid generation
Interleukin-8	Neutrophil attraction
Platelet activating Factor	Causes hypotension in anaphylaxis and further mast cell degranulation
Peptides/proteins	
Corticotropin-releasing hormone	Inflammation, vasodilatation
Endorphins	Analgesia, vasodilatationa
Endothelin	Sepsis
Bradykinin	Inflammation, pain,
Neurokinin	Inflammation, pain
Renin	vasoconstriction
Angiotensin-I	Vasoconstriction
Somatostatin	Anti-inflammatory
Substance P	Inflammation, pain
Vasoactive Intestinal Peptide	Vasodilatation
Vascular endothelial growth factor	Neovascularization, Vasodilatation

Table 2. Classification of mast cell disorders.

Cutaneous Mastocytosis	1a. Diffuse cutaneous mastocytosis
	1b. Maculopapular mastocytosis (Urticaria Pigmentosa)
	1c. Cutaneous mastocytoma
Systemic Mastocytosis	2a. Indolent systemic mastocytosis
	2b. Smoldering systemic mastocytosis
	2c. Advanced Systemic Mastocytosis
	2d. Mastocytosis associated hematological neoplasia or Mast cell leukemia
	2e. Non-clonal disorders associated with mast cell sarcoma
Mast Cell Activation Syndrome	3a. Primary Mast cell Activating Syndrome/Monoclonal Mast Cell Activating Syndrome/Clonal Mast Cell* Activating Syndrome
	3b. Secondary Mast Cell Activating Syndrome (IgE-mediated allergy)
	3c. Idiopathic Mast Cell Activation Syndrome (no obvious etiology)
	3d. Combined primary disorder with allergy-triggered mast cell activation
Idiopathic Anaphylaxis	4a. No obvious allergens
	4b. Idiopathic anaphylaxis associated with bone marrow mastocytosis + Clonality*
	4c. Idiopathic anaphylaxis associated with Clonal mast cells* or hereditary alpha-tryptasemia
Associations of hymenoptera venom and clonal mast cell disease	5a Mastocytosis and clonal mast cells*
	5b Mast cell activation syndrome ± clonal mast cells*
	5c Bone marrow mastocytosis
	5d Heredity alpha tryptasaemia ± mastocytosis or clonal cell syndrome*
Combined Disorders	Various combination of above conditions
	*clonal mast cells associated with D816V mutation
	aberrant mast cells associated with CD2 or CD25 surface marker

The role of chymase in anaphylaxis is presently underestimated. It is a serine protease present in the mast cells of the heart, blood vessels, skin, and gut. In the skin, 98% of mast cells produce chymase compared with only 7% of pulmonary and bronchial mast cells. Chymase is stored in secretory granules bound to its inhibitor heparin and was believed to be rapidly degraded by proteases following its release. However, it now appears that it is rapidly captured by circulating alpha-2 Macroglobulin and sequestered within a cage-like structure that precludes its detection in standard assays, limits access to inhibitors, and allows access to the systemic circulation [46]. The Chymase/alpha-2 Macroglobulin complex remains accessible to small substrates like Angiotensin-1 where Chymase plays a role in systemic BP control that could also protect against cardiovascular collapse following massive mast cell mediator release. Newer assays can detect captured Chymase and suggests a steady leak of chymase from mast cells as responsible for the background production of Angiotensin-II. This in turn can stimulate vasoconstriction of the blood vessel smooth muscle cells and is thought to account for up to 80% of the circulating angiotensin-II levels and blood pressure control [47–50]. Importantly, chymase can hydrolytically inactivate peptides such as Bradykinin, kallikrein and substance P.

Mast cell heparin released with chymase activates the ‘contact system’ with auto-activation of clotting factor XII leading to activation of Factor X-mediated Bradykinin formation. Unsurprisingly, heparin is linked to circulating Bradykinin levels and the severity of anaphylaxis [51–55]. In mice

deficient in factor X and bradykinin, systemic anaphylaxis does not produce hypotension or death, indicating an important role for these mediators in severe reactions (Figure 1).

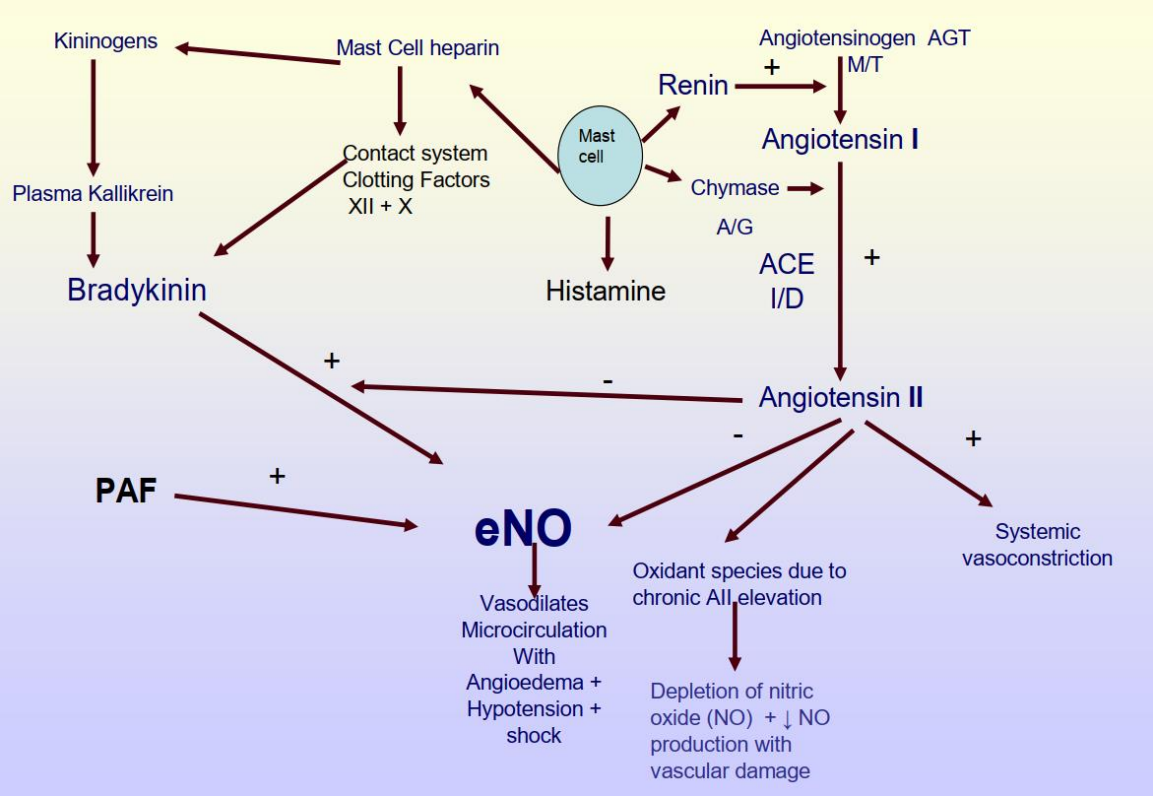

Figure 1. Renin-angiotensin system.

Rodent studies, suggest that platelet-activating factor (PAF) is also involved in anaphylaxis-induced cardiovascular collapse [56] that can be prevented by PAF antagonists [57,58]. In PAF-knockout mice, neither hypotension nor death in anaphylaxis occurs. However, PAF levels have been measured in man, and are reduced immediately following anaphylaxis, but are normal if measured away from the event [56,58]. PAF has been shown to further enhance mast cell histamine release and anaphylaxis in wildtype mice can be blocked by anti-histamines and a PAF antagonist. Animal models examining the depletion of monocytes and macrophage in anaphylaxis, suggests that they may also be the source of PAF along with mast cells [14,59,60]. PAF, like bradykinin may also act through endothelial nitric oxide (eNO) when mediating its hypotensive effect in anaphylaxis, as the nitric oxide -inhibitor L-NAME (L-Nitro Arginine Methyl Ester) can block severe hypotension and death induced by PAF. Endothelial NO is now of interest in murine models of anaphylaxis, where chronic blockade of eNO does increase the expression of mRNA for renin, ACE, and ATR1-receptors in the aorta suggesting a relationship [61]. Endothelial nitric oxide is a critical mediator of shock and death in animal models [62,63] and can be attenuated/prevented by endothelial nitric oxide inhibitors. Bradykinin also exerts a powerful arterial vasodilating effect on the microcirculation through stimulation of nitric oxide synthase that produces endothelial nitric oxide (eNO) (Figure 1).

2.4. Delayed release and newly synthesised mediators

In a more delayed manner MC activation leads to the release of several newly synthesised mediators such as prostaglandins and leukotrienes [64,65]. These encourage smooth muscle contraction and mucous formation that are central to the reduced bronchial airflow and asthma symptoms. Platelet activating factor (PAF) is also produced in a similar time frame [56] as are several cytokines including IL-1β, IL6, IL31, IL33 [66,67], and TGFβ amongst many others. Interestingly, several of these cytokines activate and stimulate the secretion of others in an amplification of inflammatory pathways. In this regard, TGFβ can encourage Th17 cells [68] that promotes inflammation and IL-33 amplifies the effect of IgE on histamine release from mast cells and basophils [69–71]. IL33 also stimulates MCs to secrete IL-1β, which then fuels IL6 production to promote inflammation [72]. Additionally, IL33 has also been shown to boost the facility of substance P (SP) to stimulate secretion of vascular endothelial growth factor by MCs and without inducing obvious degranulation [73]. IL31 is especially relevant to allergic symptomatology as it is highly potent at inducing itching [74] and thus adds to the pruritus caused by histamine and cutaneous discomfort produced by SP. Interestingly, activated MCs can also synthesise and secrete chemokines CCL2 and CCL8 that are important in inflammatory cell recruitment [75]. MC activation through FcεR1 can also stimulate autocrine hemokinin-1 synthesis and release, which via neurokinin 1 receptor stimulation can increase MC mediator release [76] and encourage renin production [77] with the latter being important in countering the hypotension of anaphylaxis.

2.5. Non-IgE stimulants of mast cell activation

MCs are not infrequently activated by specific IgG binding to FcγRII/III, activated complement proteins C3a/C5a binding to complement receptors CR3 and CR5 and by several low molecular agents [65]. The latter include several drugs [78–80], organophosphates, heavy metals, and specific neuropeptides such as corticotropin-releasing hormone [81], neurotensin (NT) [82,83], and substance P (SP). In the case of drug induced allergy/anaphylaxis, the reactions are often seen with the first dose. The increase in the occurrence of severe allergic reactions during periods of stress may be explained by the complex interaction and facilitation of MC activation by neuropeptides and these agents [84,85]. In regards to drug mediated allergic reactions, there is now abundant evidence supporting the importance of the low affinity G-protein-coupled receptor MRGPRX2 [86]. This becomes especially relevant in reactions occurring during anaesthesia and which cannot be identified following extensive skin prick and intradermal testing. Recent evidence also implicates this receptor in aetiology of chronic prurigo [87]. Reactions to opiate painkillers and codeine is thought to be through the surface mast cell opioid μ-receptor. These reactions often present with early itching and rash but maybe more florid in some cases but generally are easily treated with anti-histamines and steroids [88,89].

Reactions following intravenous radiocontrast injections and nanotechnology drugs (liposomal or micelle-solubilized drugs) [90] involve complement activation by direct complement C3 adsorption with conformational changes that resemble C3b, from which onward downstream complement activation of C3b convertase occurs. Occasionally, IgG + IgM antibodies are present or the complement component C1q is directly activated by the liposome [91]. Drugs in this category include the anti-fungal drug amphotericin (ambisome) and many chemotherapy drugs related to Taxol. Complement activation can be via the classical, lectin, or alternative pathway all of which can activate

Complement C3a and C5a giving surface activation of the mast cell and basophil surface complement receptors and mediator release [92,93]. C3a and C5a can induce respiratory distress with bronchoconstriction by direct binding to specific C3a and C5a receptors expressed on bronchial smooth muscle and epithelial cells in both mice and human lungs [92,93]. These anaphylatoxins (C3a and C5a) stimulate chemotaxis and mobilization of intracellular free Ca2+ in mast cells with C5a causing the rapid release of histamine and tryptase from mast cells.

3. Factors influencing mast cell activation and anaphylaxis

3.1. Blocking IgG antibodies

It is unclear why some individuals with allergen specific IgE experience life-threatening reactions while others have no symptoms. In this respect a possible protective effect of allergen-specific IgG which has a much higher concentration than allergen specific IgE has been discussed [94]. Elevation of allergen specific IgG4 is well described following both airborne allergen and venom immunotherapy even though its exact role is unclear. With food allergy, allergen-specific IgG levels are higher in individuals that are sensitized but unresponsive to the allergen or no longer respond to the food allergen as a result of oral allergen desensitization. Animal studies have demonstrated the presence of allergen specific IgG can inhibit the production of specific IgE by promoting the induction of T-regulatory cells to reduce immune responses. The factors driving IgE and IgG responses to ingested antigens are complex and not yet fully understood, but the gut microbiome may have an important role. Human and mouse MC and basophils express Fcg receptors (FcgR's) that bind to IgG antibodies and their patterns of expression vary among leukocytes [95–97]. Unlike humans, mice monocytes appear to express FcγRI but do not express FcγRIIB, which is expressed by human B cells and basophils. Further, important differences include expression of FcγRIIIA by humans but not mice but is limited to NK cells and monocytes/macrophages. Additionally, FcγRIV exists in mice but not in humans and FcγRIIA, FcγRIIC and FcγRIIIB exist in humans but not in mice. Overall, however, human mast cells and basophils are believed to express two IgG receptors (FcgRIIa and FcgRIIb) with FcgRIIb believed to be an inhibitory IgG receptor able to reduce activation of the mast cell and this is a focus for future research [98].

3.2. Oestrogen

Oestrogen's role in allergic disease was initially suggested by rodent studies [99]. Clinically, allergic disease is three times more common in females and more active especially during their peak reproductive years [100]. Furthermore, 30–40% of women with asthma have observed increased symptoms in the pre-menstrual phase when oestrogen and progesterone levels are changing and leukotriene C4 levels are shown to be elevated [101,102]. Mechanistically, human mast cells have mRNA for oestrogen receptor α but not β [103] and basophils and mast cells pre-incubated with physiological concentrations of oestrogen show increased histamine release following IgE cross-linking of the surface receptor [99] with mast cells similarly exposed undergoing partial degranulation. As expected this could be blocked by tamoxifen, suggesting a direct link to an oestrogen receptor [101]. Finally, the severity of anaphylaxis may be greater in females as oestrogen has an inhibitory effects on ACE biosynthesis [104,105] (see later).

3.3. Vitamin D

The role of Vitamin D in allergic and immune disease is interesting [106,107]. In the United States, prescriptions for auto-injecting adrenaline pens for anaphylaxis is 4-fold higher in the northern US states than the southern states where Vitamin D levels are lower from reduced sunlight exposure. Case reports also show benefit in reducing the symptoms of physical urticaria following supplementation of Vitamin D for severe cases. This benefit may be explained by ability of vitamin D3 to stabilize mast cells and reduces IgE dependant pro-inflammatory mediator release including reduced histamine release [108,109]. Moreover, 1,25 dihydroxy-Vitamin D receptors are present on mast cells, macrophages, T and B lymphocytes and other antigen presenting cells and it appears important for the functioning of the glucocorticoid receptor. Micro-array studies show that within the CD4+ T-lymphocyte alone, a total of 102 genes are targeted by Vitamin D with 57 being down-regulated and 45 up-regulated [110,111]. Within the skin, the presence of inflammation and inflammatory cytokines increases the local production of 1,25 hydroxy-Vitamin D usually by macrophages, which then reduces the production of inflammatory cytokines (including Interleukin-6,8,12,17,23 and tumor necrosis factor-α) along with the infiltration of neutrophils and eosinophils into the skin [112,113].

3.4. The renin-angiotensin system

In the early 1990s, Hermann and Ring showed a stepwise reduction in renin and angiotensin levels in patients with increasing severity of hymenoptera venom anaphylaxis (grade 1–3) [114,115]. Subsequently, Summers et al. [116] showed that patients with serum ACE levels below 37 mmol/L were 9.7 times more likely to develop pharyngeal oedema than those with mean serum ACE levels above 47 mmol/L [116]. With the widespread use of ACE-Inhibitor drugs, case reports of prolonged and profound anaphylaxis have appeared in the literature from the early 1990's [117]. Importantly, the ACE gene exists in 2 allelic forms, with the presence of "I" (insertion) or its absence "D" (deletion) of a 287 base pair intron of the gene. The "D" genotype is associated with higher ACE activity and AII levels and increased plasma bradykinin catabolism and individuals with the homozygous DD genotype have the highest serum ACE levels while the I/I or I/D genotype has the lowest serum ACE and AII levels [118]. In this respect, Niedoszytko et al. [119] showed 80% of 30 patients with insect venom allergy of grades 3–4 on the Mueller scale [120] had the ID or II genotypes along with 50% lower levels of serum ACE activity and higher basal bradykinin levels. Similarly, we found II/ID genes linked to anaphylaxis involving hypotension and angioedema and associated with lower serum ACE levels relative to both atopics and healthy controls [118]. This may be explained by serum ACE being important in the catabolism of bradykinin, which can cause angioedema and hypotension [121] (Figure 1). Additionally, we noted that gene polymorphisms that coded for low activity of RAS were more prevalent in severe anaphylaxis [118]. These genes included ACE, Renin, angiotensinogen, angiotensin Receptor-1, Chymase, and the bradykinin B2-receptor gene [122].

4. Diagnosing mast cell dysfunction and anaphylaxis

The clinical history is critical and aims to check for the symptoms and signs related to the release of mast cell mediators previously discussed. The clinical features of anaphylaxis need assessment as

well as a search for any causative and contributory factors for mast cell activation such as alcohol ingestion, exercise, NSAID usage, and stress. However, activated mast cells release tryptase and detecting raised serum levels 2–4 hours later can be very helpful in suspected anaphylaxis. In contrast, the release of mast cell chymase in allergic reactions is largely overlooked but warrants discussion. Blood Chymase levels increase after 1 hour following allergic reactions and remain raised for 8–24 hrs. Autopsy studies show mean Chymase blood levels of 89.8 ng/mL in anaphylaxis compared with <3 ng/mL in cases without anaphylaxis [123,124].

5. Mast cell disorders

5.1. Broad categorization

Disorders arising from mast cell mediator release may be differentiated into those with increased numbers of mast cells (mastocytosis) and those with aberrantly raised function (mast cell activation syndrome) (Table 2). There is, however, a continuum of variation between the two that influences the clinical presentation and especially with features of anaphylaxis [23,125] and especially idiopathic anaphylaxis [126]. Notwithstanding, genetic and hormonal predisposition is likely important [125,127–129] as is the circadian facility of MC mediator release [41,130].

From a clinical perspective, three sets of criteria are required to suggest a mast cell problem [23,126,127].

(1) Episodic symptoms of mast cell activation eg itchy rashes, flushing, bronchospasm, abdominal discomfort and diarrhoea, faintness/syncope etc.

(2) Laboratory evidence of released mast cell mediators in blood and urine related to these episodes such as raised serum tryptase levels at baseline and within 4 hours of an acute event.

(3) Symptomatic improvement after regular MC mediator antagonist therapy, MC reduction, and/or stabilizing treatment.

5.2. Mastocytosis

Here there is clonal proliferation of mast cells in several organs, including the skin (urticaria pigmentosa, maculopapular areas, or mastocytomas), bone marrow, and gastrointestinal tract, (liver, spleen, lymph nodes). This is usually caused by mutations of the c-KIT receptor [131] that potentiates mast cell activation by IgE and non-IgE receptor mechanisms. There is also constitutive activation of the MC with mediator release leading to systemic symptoms and even anaphylaxis. Somatic missense mutation involving substitution of aspartic acid (D) to valine (V) at amino acid B16 in exon 17 is the most frequent mutation but others are also recognized. C-KIT binding to the stem cell factor receptor (a tyrosine kinase receptor) initiates a signaling cascade within the mast cells that regulates their growth, migration, and proliferation. In consequence, increased c-KIT activity can be associated with increased mast cell numbers (mastocytosis) and neoplastic disorders of mast cell expansion in man due to its oncogene properties [131,132]. In addition to c-KIT, there are also other markers of mast cell irritability including CD25 (alpha chain) of the IL-2 receptor or CD2 (lymphocyte function antigen-2) present on neoplastic mast cells. More variants will no doubt be described but the exact details of how this makes the mast hyperactive are currently sketchy [133,134].

The World Health Organization has classified mastocytosis into 2 major groups:

1. Cutaneous mastocytosis
2. Systemic mastocytosis (involving at least 1 extracutaneous organ**)**.

The true prevalence of mastocytosis is unknown and probably goes unrecognized in milder cases, but is estimated to be 9–13 per 100,000 [135,136]. Cutaneous mastocytosis is commonest in young children and is often a skin-limited disease that regresses with time. Fuchs et al. [137] have proposed a scoring system allowing the prediction of systemic mastocytosis (SM) in those with cutaneous mastocytosis and based on the tryptase level as well as constitutional/cardiovascular symptoms and bone pain/osteoporosis. In adults, multi-organ involvement is more common, can be checked by biopsy examination of skin and the bone marrow, and may give more symptoms with a possible progression to mast cell leukemia. This was considered more likely in the presence of activating C-kit and a range of other mutations [138] which clearly affects prognosis [139]. Regardless, 85% of subjects with SM the condition is indolent and symptomatic patients have local or systemic episodes of mast cell mediator release (including histamine, proteases, leukotrienes, and prostaglandins). Often, there are recognized triggers for the "Mast Cell Release Episodes" such as physical exertion, heat and cold, insect stings, alcohol consumption, oral non-steroidal anti-inflammatory drugs, and emotional distress. Specific triggers vary between patients but generally symptoms predominately include flushing, pruritus, palpitations, dizziness, hypotension, and syncope. Additional reported symptoms may include breathing difficulties, abdominal pain and diarrhea. A history of flushing is a cardinal symptom in many of these patients that should alert suspicion. Some subjects may experience symptoms resembling anaphylaxis that may last 15–30 minutes although some episodes may be life threatening due to severe hypotension [23,126,135].

5.3. Secondary Mast cell activation syndrome

Secondary MC activation through IgE and non-IgE-mediated processes (food, drugs, venom) can produce variable allergy type symptoms and systemic anaphylaxis without evidence of a clonal mast cell population and without evidence of a primary mast cell activation disorder. Symptoms are episodic and similar to those seen in mastocytosis as detailed above [23,140,141]. Interestingly, there is evidence that MC irritability leading to non-allergic mediator release is more frequent in those with joint hypermobility syndrome [142,143] although the precise mechanism of this association has yet to be defined. While a number of non-allergic symptoms such as fatigue, headaches, myalgia etc have now been associated with this secondary MCAS, these are unlikely to be due to the release of preformed mediators but may possibly arise from inflammatory cytokine release [143]. Regardless, the diagnosis of MCAS is based on a combination of several suggestive symptoms in the clinical history supplemented by urine tests looking for elevated levels of methylhistamine, leukotriene E4, and 2,3-dinor-11beta-prostaglandin F2 alpha [144]. The precise role of gastrointestinal dysbiosis, increased permeability of the intestinal epithelium and the absorption of microbial factors able to stimulate MCs and leading to constitutional symptoms and allergic type rashes is certainly interesting and warrants further in depth investigation [145].

5.4. Hereditary alpha-tryptasaemia

This is found in 5–6% of the general population and is an autosomal dominant condition producing excess copies of the alpha-tryptase gene (TPSAB1). It is a common cause of elevated basal

serum tryptase levels >8 ng/ml, due to raised pro-alpha tryptase synthesis rather than increased mast cell activation [146,147]. It is associated with some increase in of mast cell numbers in the bone marrow and gut and some increase in the urinary excretion of mast cell mediators such as methylhistamine, 9α-11β-Prostaglandin F2 and the breakdown product PGDM. Its prevalence is increased in both clonal and non-clonal disease suggesting an assessment of its presence is made in the evaluation of mast cell disorders [148]. The risk for severe spontaneous or insect venom-triggered anaphylaxis is reported to be increased in this condition [149,150].

6. Treatment options for anaphylaxis and mast cell disorders

Adrenaline is first line for acute anaphylaxis [151–153] in mast cell disorders. In refractory cases of severe hypotension not responding to repeated doses of intramuscular epinephrine or where cardiac arrest has occurred, intravenous epinephrine should be given with continuous monitoring of the cardiac response, blood pressure, and oxygen saturation. Anti-histamines, oxygen and fluid replacement should be given once the cardiovascular status is stabilized then beta2-agonists and corticosteroids are usually recommended [153].

Long term management is aimed at the prevention of repeat episodes of anaphylaxis including specific IgE and skin tests for any potential triggers and discussion of foods, medication, inhalational triggers and cofactors such as alcohol, exercise, and non-steroidal anti-inflammatory drugs (NSAIDs) to be avoided. Elimination of histamine-rich foods is not routinely recommended. Those sensitized to venom should have at least 3 years and in some cases lifelong venom immunotherapy to reduce recurrent anaphylaxis risk following a sting [154].

There are no randomized studies to show which prophylactic therapy options are superior for mastocytosis. A stepwise approach is important with step one utilizing increasing doses of oral antihistamines (H 1 receptor blockers) up to 4 times standard levels if required. Histamine receptor-2 blockers and anti-leukotrienes drugs can be added, with oral sodium cromoglycate and corticosteroids if patients remain unresponsive. If these combination therapies are ineffective, then omalizumab, the humanized monoclonal antibody that specifically binds to free IgE, can be used and has been shown to diminish the frequency of anaphylactic reactions in a case series [155] ‘Cytoreductive’ therapy can be used in systemic mastocytosis, which now commonly employs one of the tyrosine kinase inhibitors to target the mast cell growth receptor c-KIT. Both midostaurin and avapritinib are currently approved for this treatment and may give prompt resolution of recurrent anaphylaxis although side effects are not infrequent [156] (Gotlib et al, 2021). There are also reports that this treatment reduces splenomegaly and also bone marrow mast cell numbers in cases with advanced systemic mastocytosis [157,158].

7. Conclusions

The mast cell and its role in allergic and indeed non-allergic diseases as well as its wide distribution throughout the body, including the myocardium, central nervous system, and elsewhere continues to expand its importance in a diverse range of human illnesses. Much has been written about the early and rapidly acting mediators released by activated MCs in the context of localized and systemic allergic reactions. However, there is increased appreciation that they synthesize and release a wide range of inflammatory cytokines that can perpetuate inflammation and perhaps also explain the constitutional symptoms seen in association with allergic reactions and help clarify its role in stress

and non-parasitic infections. The data on environmental, menstrual, circadian, and psychological factors influencing the onset and severity of anaphylaxis needs further investigation with its links to mast cell disorders in which normal numbers of MCs appear to be more irritable and prone to activation by life factors and agents that are normally tolerated. The precise role of specific MC receptors such as the MRGPX2 in this irritability needs definition. Consensus on the exact clinical and laboratory features of idiopathic mast cell activation syndrome is urgently needed to avoid this term being used for all illnesses with vague symptoms in which a cause is not apparent. This may open a new chapter in human diseases and mast cell regulation. The increasing incidence of anaphylaxis within a relatively short time frame also needs to be explained in terms of rising stress levels, dysbiosis in the gastrointestinal tract, and increased use of additives and colorings in food. It would certainly be more helpful to delineate the precise mode of interaction between immune genes and the environment.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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